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TO:	Examiner Michael C. Wilson Examining Group 1632	**FROM:**	Glenn P. Ladwig Patent Attorney Registration No. 46,853
COMPANY:	United States Patent and Trademark Office	**DATE:**	September 27, 2005
FAX NO.:	571-273-8300	**NO. OF PAGES (INCLUDING COVER SHEET):**	37

SUBJECT/MESSAGE:

Re: U.S. Patent Application Docket No. GJE-21D2
NEURAL TRANSPLANTATION USING PLURIPOTENT NEUROEPITHELIAL CELLS
Serial No.: **09/760,274**; Date filed: January 12, 2001
Applicants: Sinden, Gray, Hodges, Kershaw, Rashid-Doubell

Submission to PTO:
1. **Duplicate copy** of Appeal Brief submitted March 21, 2005, excluding references
2. Copy of return receipt post card for Appeal Brief submitted March 21, 2005

In a telephonic conference with Glenn P. Ladwig, Examiner Wilson requested a **duplicate copy** of the Appeal Brief submitted March 21, 2005 (excluding references) and a copy of the return receipt post card.

If you do not receive all pages or if any transmission is not legible, call the sender at (352) 375-8100.

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March 21, 2005

DOCKET NO.: GJE-21D2

SERIAL NO.: 09/760,274

DATE FILED: January 12, 2001

APPLICANTS: Sinden et al.

SUBMISSION TO PTO:
1. Transmittal Letter in triplicate
2. Petition and Fee for Extension of Time in triplicate
3. Appeal Brief under 37 CFR 41.37 including Appendixes A-B

mv

APPEAL BRIEF
EXAMINING GROUP 1632
Patent Application
Docket No. GJE-21D2
Serial No. 09/760,274

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Michael C. Wilson
Art Unit	:	1632
Applicants	:	John Sinden, Jeffrey A. Gray, Helen Hodges, Timothy Kershaw, Fiza Rashid-Doubell
Serial No.	:	09/760,274
Filed	:	January 12, 2001
For	:	Neural Transplantation Using Pluripotent Neuroepithelial Cells

MS APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed:
Commissioner for Patents, P.O. Box 1450
Alexandria, VA 22313-1450 on March 21, 2005.

Glenn P. Ladwig
Glenn P. Ladwig, Patent Attorney

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TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

This application is owned by ReNeuron Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences. Accordingly, no Related Proceedings appendix is part of the Brief.

III. STATUS OF CLAIMS

Claims 57, 58, 60-62, 64, and 76-86 are pending in the application and are under final rejection. Claims 1-48, 59, and 68-75 were cancelled in the Amendment dated February 20, 2004. Claims 49-56 were cancelled in the Amendment dated September 30, 2002. Claims 63 and 65-67 were cancelled in the Amendment dated March 20, 2003. The rejections of claims 57, 58, 60-62, 64, and 76-86 are appealed herein.

IV. STATUS OF AMENDMENTS

A Response to the final Office Action dated May 25, 2004, was filed on October 21, 2004. The Response of October 21, 2004 was entered. Claims 57, 58, 60-62, 64, and 76-86 are currently pending and attached hereto as Appendix A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 57, 81, and 85 are independent. Appellants' invention pertains to novel methods for treating a disorder associated with damage to, or loss of, brain cells in a mammal, by intracerebrally transplanting pluripotent, nestin-positive, neuroepithelial cells into the brain of the mammal, thereby improving the mammal's brain function. Intracerebral transplantation is discussed at page 14, lines 16-32, of the specification of application Serial No. 09/760,274, hereinafter referred to as the '274 application. The cells to be transplanted in each of claims 57, 81, and 85 are pluripotent and conditionally immortal. As "pluripotent" cells, they have not yet completed differentiation into a specific, terminally differentiated cell type, instead having the potential to further differentiate into different types or different phenotypes of cell (see, for example, page 1, lines 22-30, of the '274 application). The pluripotent cells are nestin-positive, as taught in Example 4, at page 20, lines 4-37, and page 21, lines 1-10, of the '274 application.

Further, these cells have been genetically modified to be conditionally immortal, such that they are immortal prior to transplantation and differentiate after transplantation (see, for example page 5, lines 32-36; page 6, lines 1-36; page 7, lines 1-7, and page 12, lines 23-31, of the '274 application). One method of rendering the cells conditionally immortal is by transduction of an oncogene, such as the temperature-sensitive simian virus 40 large T antigen, described at page 9, lines 1-13, of the '274 application, and recited in claims 81 and 85. The oncogene may be under the control of a promoter such as the interferon-inducible H-2K^b promoter, recited in claim 85. The pluripotent cells may be human cells, as taught at page 7, lines 8-10, and page 13, lines 12-16, of the '274 application, and recited in claims 81 and 85. When transplanted into the brain of a mammal suffering from a disorder associated with damage to, or loss of, brain cells, the pluripotent neuroepithelial cells respond to signals from the affected brain by taking up a phenotype that is able to replace or compensate for the functional deficit caused by the damage or loss of brain cells (see page 5, lines 10-24; page 10, lines 34-36; and page 11, lines 109, of the '274 application).

Transplantation of conspecific fetal neural tissue into a damaged brain has been studied previously in animal experiments and consequent repair has been observed at the neuroanatomical, physiological and behavioral levels (see, for example, page 4, lines 28-32, of the '274 application). Widespread use of this work within the context of Parkinson's disease has been frustrated by the need for tissue derived from conspecific fetal brain, *i.e.*, the fetal tissue required must be specific to the type of damage intended to be repaired and it must be harvested at a precise, time-limited stage during brain development that varies with brain region and cell type. Hence, the requirement for specific matching of cell types leads to both practical and ethical problems (see, for example, page 5, lines 1-9, of the '274 application). Appellants discovered that when conditionally immortal, pluripotent, nestin-positive neuroepithelial cells are implanted into a damaged brain, the cells differentiate into the appropriate cell type required to repair the brain, and the differentiated cells are able to form the appropriate neural connections required to improve function. Thus, it is not required that the pluripotent cells be obtained from the same region of the brain as the damaged region. However, this may also be done. For example, claim 85 recites that the deficit is caused by damage to the hippocampus and the pluripotent cells are hippocampal cells. The phenotype of the differentiated cells may be the same phenotype as the damaged or lost cells, or may be a different phenotype, or a number of

phenotypes. In any case, the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells (see, for example, page 5, lines 10-22, of the '274 application). Furthermore, once they are transplanted, pluripotent neuroepithelial cells have the ability to migrate extensively, seeking out damaged tissue and functionally integrating. This facilitates repair in situations where the damage is widespread or where the locus of the damage is not entirely known (see, for example, page 7, lines 21-36; page 8, lines 1-10; and Example 9 of the '274 application).

Because of the cells' plasticity and migration capability, one clonal pluripotent cell line can repair damage in a number of different areas of the brain, and if more than one particular neural cell type is required to repair damage in a given area, then a single pluripotent cell line will be capable of differentiating into the different types of neural cells required to achieve repair. Thus, the present invention provides both a strategy and a material basis for transplant therapies with which to target a wide range of behavioral and psychological deficits caused by an equally wide range of forms of damage to the brain. For example, the methods of the invention may be used to treat a cognitive deficit, as recited in claim 85 (see, for example, page 9, lines 29-35; page 10, lines 1-9; and Examples 5-9 at pages 22-29 of the '274 application).

VI. GROUNDS OF REJECTION

A. Claims 57, 58, 60-62, 64, and 76-86 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description.

B. Claims 57, 58, 81, 82, 85, and 86 stand rejected under 35 U.S.C. § 112, first paragraph, as new matter.

C. Claims 57, 58, 60-62, and 76-86 stand rejected under 35 U.S.C. § 112, first paragraph, as non-enabled.

VII. ARGUMENT

A. The specification provides sufficient written description of that which is essential to obtain human pluripotent, nestin-positive neuroepithelial cells capable of improving brain function resulting from damage to, or loss of, brain cells.

Claims 57, 58, 60-62, 64, and 76-86 stand rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. As an initial matter, in the final Office Action dated May 25, 2004, the Examiner indicated that the rejection of claims 57, 58, and 60-62, for lack of written description, regarding transplanting "human" pluripotent, nestin-positive neuroepithelial cells has been withdrawn because the term "human" has been deleted (page 6, lines 17-20). Appellants note that claims 57, 58, and 60-62 have not been amended subsequent to the final Office Action; nonetheless, the Advisory Action dated December 21, 2004 included claims 57, 58, and 60-62 in the instant rejection under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. Appellants are understandably perplexed by the apparent inconsistency in the stated disposition of the claims under this rejection.

In the final Office Action dated May 25, 2004 and the subsequent Advisory Action dated December 21, 2004, the Examiner indicates that the '274 application does not provide an adequate written description of a method of using human, nestin-positive, neuroepithelial cells for treating a cognitive deficit in humans because the specification does not adequately describe the human cells capable of treating a cognitive deficit.

> Thus, claiming a method of treating cognitive deficit using pluripotent, nestin-positive neuroepithelial cells in humans without defining the properties required to obtain human cells capable of treating a cognitive deficit or how to use mouse cells to treat humans is not in compliance with the written description requirement (emphasis added; Office Action dated May 25, 2004; page 8, lines 17-21).

> The nestin-positive, musashi-positive, human, pluripotent, neural precursor cells described in the Declaration by Dr. Sinden as having the desired function in vivo have a narrower scope than nestin-positive, human, pluripotent, neural precursor cells described in the specification as originally filed. As such, applicants did not adequately describe that which was essential to obtain human neural precursor cells having the desired function, i.e., nestin-positive neural precursor cells expressing musashi. The experimental results in the Declaration by Dr. Sinden remain unpersuasive because the cells used in the experiment were of a narrower scope than those described in the specification as originally filed

> and because musashi expression may be essential to obtain nestin-positive neural precursor cells with the desired function in humans (emphasis in original; Advisory Action dated December 21, 2004; page 3, lines 5-15).

The Office Action states that the '274 application teaches using mouse cells to restore cognitive function and suggests the use of human cells isolated at about eight weeks gestation. The Office Action cites the Gray *et al.* publication (*Philosophical Transactions of the Royal Soc. London*, 1999, 354(1388):1407-1421) as showing that fully differentiated hippocampal cells not yet having axons are essential to the invention, that the isolation of suitable cells must be taken at fifteen weeks gestation, and that this is essential to obtain the required amount of differentiation. However, the passage in the Gray *et al.* publication relied on by the Examiner concerns an overview of conventional transplantation methods using fully differentiated cells, not the pluripotent nestin-positive cells used in the method of the invention. When transplanting differentiated cells, it is clearly important that the correct phenotype of cell be selected for transplantation. Therefore, Appellants respectfully submit that the Examiner's interpretation and extrapolation of the teaching of Gray *et al.* to the pluripotent cells used in the present invention is incorrect.

In contrast to differentiated cells, which the prior art teaches must be conspecific, the cells of the present invention are pluripotent and have the ability to differentiate into different phenotypes, depending on external factors. Upon transplantation, the pluripotent cells are stimulated to differentiate into the desired phenotype (see page 5, lines 10-24, of the '274 application). Therefore, controlling differentiation is not an issue for the conditionally immortal pluripotent neuroepithelial cells used in the methods of the subject invention.

At page 10, the Office Action dated May 25, 2004 states that the applicants do not provide an adequate written description for the human equivalent of the mouse, nestin-positive cells capable of treating cognitive function. However, the subject specification teaches that the pluripotent cells used in the claimed method should be isolated early enough in the developmental pathway that they retain the ability to differentiate into the desired brain cell phenotypes (page 13, lines 7-11, of the '274 application). It is well known by those skilled in the art that the plasticity (*e.g.*, pluripotency) of embryonic cells is generally inversely related to the age of embryonic development. Therefore, if nestin-positive pluripotent cells are obtainable from a human at 12 weeks gestation (as proven in the Sinden Declaration), it is at least as likely,

if not more likely, that the cells would be obtainable from a human at an earlier stage of development, for example, at 8 weeks, as suggested in the '274 application.

As indicated at page 13, lines 5-7 of the '274 application, the region of the brain from which neuroepithelial cells are obtained and the precise time (stage and development) they are obtained may vary. Appellants point to the Declaration under 37 C.F.R. §1.132 by Dr. Sinden, dated September 27, 2002, including Exhibits A-D, of record, which accompanied the Amendment submitted on September 30, 2002. Exhibit D describes an experiment in which human pluripotent neuroepithelial cells were isolated from the fetal cortex, conditionally modified using techniques described in the '274 application (page 6, lines 11-31, and page 12, lines 10-23), and implanted into the brains of rats having unilateral basal forebrain excitotoxic lesions, a model recognized in the art as one which mimics cell loss that occurs in Alzheimer's disease and other neurodegenerative diseases. Restoration of function was assessed using a water maze test, wherein poor performance across several parameters reflects spatial long-term and short-term learning and memory impairments. The human cell line was assessed in comparison with the murine MHP36 cell line (a cell line exemplified in the '274 application) as a positive control, and with sham-grafted lesioned and non-lesioned controls. Non-lesioned controls received vehicle at the same sites. Rats grafted with the murine MHP36 cell line performed significantly better than lesioned animals. However, rats receiving cells of the human cell line showed as rapid spatial learning as non-lesioned controls, and were superior both to the lesion-only group and the murine-grafted group. The Sinden Declaration shows that pluripotent nestin-positive neuroepithelial cells can be obtained from human fetal cortex at 12 weeks gestation and restore function (see paragraph 9 and Exhibit D of the Sinden Declaration). Thus, page 13, lines 5-16, of the '274 application highlights 8 weeks as an example of when such pluripotent cells can be isolated. The human cells can also be isolated at 12 weeks (as demonstrated by Exhibit D) and even later, depending on the brain region from which cells are obtained. As will be appreciated by one of ordinary skill in the art, the hippocampus and cortex are properly identifiable as anatomical structures at approximately 10-12 weeks, which is why the human cells were isolated at the 12-week gestation period. The human cells described in Exhibit D were taken from the cortex because the cells are readily obtainable in large numbers from this brain region. The success of the experiment described in Exhibit D using cortex cells supports the teachings of the specification that pluripotent neuroepithelial cells other than

hippocampal cells are capable of improving a brain disorder, such as cognitive deficit. Once obtained, cells can then be screened for pluripotency *in vitro*, to verify their ability to differentiate upon transplantation, as taught at page 13, lines 17-28, and Example 4, at pages 20-21 of the '274 application. The Examiner has provided no reasons to doubt that the pluripotent cells used in the claimed methods can be obtained from more than one region of the brain or at more than one gestational stage.

The May 25, 2004 Office Action cites Renfranz (*Cell*, 1991, 66:713-729) for teaching that nestin-positive pluripotent cells differentiate into different neural cell lineages. The Renfranz publication teaches the establishment of a differentiated cell line derived from embryonic precursor cells. Because the cells are pluripotent, they have the ability to differentiate into different types of neural cells, depending on environmental factors. This is consistent with the properties of the pluripotent neuroepithelial cells as taught and used in the method of the invention. Upon transplantation, the pluripotent neuroepithelial cells are stimulated to differentiate into different neural phenotypes that are capable of functionally integrating and compensating for the damaged or lost cells. As taught at page 5, lines 10-31, of the '274 application, this means that with one clonal pluripotent cell line it is possible to repair damage in a number of different areas of the brain, and that if more than one particular neural cell type is required to repair damage in a given area, then a single pluripotent cell line will be capable of differentiating into the different types of neural cells required to achieve repair. This is a major advantage of the method of the invention.

The Office Action also cites the Villa *et al.* publication (*Exp. Neurol.*, 2000, 161:67-84) as showing that properties identifying human neural stem cells are not well understood. Appellants respectfully submit that the Villa *et al.* publication supports the written description of the claimed subject matter in that it shows that one of ordinary skill in the art can obtain cells having the properties that the specification teaches are desirable. The Villa *et al.* publication is concerned with defining the optimal conditions for preparing suitable pluripotent cells and makes various statements that genetically-modified cells provide the most convenient method. The cells used in the Villa *et al.* publication are taken at approximately ten weeks gestation. Furthermore, the Villa *et al.* publication makes it clear that suitable cells can be defined in terms of nestin expression and pluripotency. These are properties of the cells that are taught in the specification and recited in the claims of the subject application. Although there is a statement in

the Villa *et al.* publication that properties identifying a human neural stem cell are not well understood, this does not mean that a human neuroepithelial pluripotent cell cannot be identified. Pages 13 and 20-21 of the subject '274 application teach how to do so. Clearly, Villa *et al.* and others in the art have done so. Although the Villa *et al.* publication was not publicly available at the time of filing, because they used the same techniques as taught by Appellants, it demonstrates that the subject specification contained all the information necessary for one of ordinary skill in the art to carry out the invention.

At page 10 of the Office Action dated May 25, 2004, the Examiner observes that the human cells used in the experiment described in Exhibit D express both nestin (intermediate filament marker) and musashi 1, and mistakenly concludes that detection of both would have been required for one of ordinary skill in the art to obtain the cells for transplantation. As indicated in Exhibit D, nestin and musashi 1 are both phenotypic markers for neuroepithelial stem cells. The musashi 1 marker was more recently identified than nestin and, hence, merely confirms the neural epithelial status of the cells, which was already shown by nestin expression. Appellants submitted the Kawaguchi *et al.* (*Molecular and Cellular Neuroscience*, 2001, 17:259-273) and Sakakibara *et al.* (*PNAS*, 2002, 99(23):15194-15199) publications to the Patent Office with their Response under 37 C.F.R. §1.116 dated October 21, 2004. The Examiner considered and commented on the Kawaguchi *et al.* and Sakakibara *et al.* publications in the Advisory Action dated December 21, 2004. The Sakakibara *et al.* publication indicates that musashi 1 is a binding protein that is expressed in neural precursor cells, and which can be used as one marker to identify precursor cells. As indicated in the abstract of the Sakakibara *et al.* publication, the musashi family of proteins are evolutionarily conserved across species. In mammals, musashi 1 and musashi 2 are strongly co-expressed in neural precursor cells, including CNS stem cells. Likewise, the Kawaguchi *et al.* publication demonstrates that nestin is another marker that is expressed in neural precursor cells. Use of musashi 1 for this purpose of identifying neural precursor cells is thus equivalent to use of nestin. One of ordinary skill in the art would appreciate that musashi 1 expression does not represent an identifying characteristic of the cells that had to be discovered before the method of the invention could be carried out; demonstrating the expression of nestin by the cells, as taught in the specification, is sufficient. The mere fact that the human cells were further characterized and it was determined that the cells expressed musashi 1, in addition to nestin, should not disqualify the experimental results and

accompanying Declaration by Dr. Sinden as probative evidence in the determination of written description and enablement under 35 U.S.C. 112, first paragraph.

The Office Action dated May 25, 2004 states that "claiming a method of treating cognitive deficit using pluripotent, nestin-positive neuroepithelial cells in humans without defining the properties required to obtain human cells capable of treating a cognitive deficit ... is not in compliance with the description requirement ... It is not sufficient to define the method as requiring cells having particular biological properties, i.e., expressing nestin and pluripotent and capable of treating humans, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of human cells capable of restoring cognitive function" (emphasis added; page 8, lines 17-22, and page 9, lines 1-3 of the Office Action). This statement presupposes that pluripotency and nestin expression are insufficient to identify populations of cells capable of repairing damage as recited in the claims. The Examiner has provided no rationale for this position and has placed no evidence on the record to support the premise. The Examiner merely observes that the human nestin-positive pluripotent neuroepithelial cells described in Exhibit D are also musashi 1-positive, and mistakenly concludes, solely on that basis, that musashi 1 expression "may be" required:

> The experimental results in the Declaration by Dr. Sinden remain unpersuasive because the cells used in the experiment were of a narrower scope than those described in the specification as originally filed and because musashi expression may be essential to obtain nestin-positive neural precursors cells with the desired function in humans (emphasis added; page 6, lines 11-15, of the Advisory Action dated December 21, 2004).

Certainly, the cells have still other characteristics that are not specified, but clearly they are not necessary to describe the cells. The Examiner confuses the possibility of further characterization with the necessity of doing so, and that is improper.

The Examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. The Examiner must have a reasonable basis to challenge the adequacy of the written description and must establish, by a preponderance of evidence, why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In rejecting a claim, an Examiner must set forth express

findings of fact, applying the necessary analysis, which support the conclusion that there is a lack of written description. This the Examiner has not done.

An applicant is not required to describe every detail of his invention. An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics that provide evidence that the applicant was in possession of the claimed invention. *Enzo Biochem, Inc. v. Gene-Probe Inc.*, 285 F.3d 1013; 62 USPQ2d 1289 (Fed. Cir. 2002) and *Enzo Biochem, Inc. v. Gene-Probe Inc., on rehearing* 296 F.3d 1316; USPQ2d 1609 (Fed. Cir. 2002) *rehearing en banc denied.* Such characteristics can include (a) complete or partial structure of the claimed invention; (b) functional characteristics, provided there is a correlation between the function and structure of the claimed invention; (c) physical properties, and/or (d) chemical properties (See, for example, "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 para. 1 'Written Description' Requirement." 66 Fed. Reg. 1099, 1106 (January 5, 2001)). The disclosure of any combination of identifying characteristics that "distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species" is sufficient to comply with the written description requirement ("Guidelines for Examination of Patent Applications under the 35 U.S.C. 112 para. 1 'Written Description' Requirement" at 1106). As indicated above, neuroepithelial cells can be screened for pluripotency *in vitro*, to verify their ability to differentiate upon transplantation, as taught at page 13, lines 17-28, and Example 4, at pages 20-21 of the '274 application. An applicant's disclosure obligation varies according to the art to which the invention pertains. The currently pending claims are drawn to methods of using cells. In addition to pluripotency, the '274 application discloses that neuroepithelial cells suitable for transplantation are nestin-positive. Immuno-detection of cell-surface markers is an art-recognized technique for the characterization of cells and determination of cell fate. There is an art-recognized correlation between cell type, *e.g.*, as determined by the cell's surface markers (the cell's chemical "structure"), and the properties and functions exhibited by the cell. The '274 application describes the recited genus of human neuroepithelial cells sufficient to distinguish the recited cells from other cells, providing sufficient characteristics by which to identify human neuroepithelial cells that may be used in the claimed invention.

Appellants respectfully submit that the '274 application provides relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise, and exact

terms that one of ordinary skill in the art would recognize that Appellants were in possession of the claimed invention. Accordingly, Appellants request that this rejection of the claims under 35 U.S.C. §112, first paragraph, be reversed.

Claims 57, 58, 60-62, 76-80, 83, and 84

In the event that the Board believes this rejection should be sustained on at least claims 64, 81, 82, 85, and 86, Appellants respectfully assert that it should certainly be overruled as to claims 57, 58, 60-62, 76-80, 83, and 84, which do not have the specific limitations that the transplanted cells are human cells or that the mammal is human. For the reasons described above, the pluripotent neuroepithelial cells described in the '274 application are representative of the class of cells recited in claims 57, 58, 60-62, 76-80, 83, and 84.

B. Claims 57, 58, 81, 82, 85, and 86 do not constitute new matter, because Appellants' specification provides support for each element of the claims.

Claims 57, 58, 81, 82, 85, and 86 stand rejected under 35 U.S.C. §112, first paragraph, in various combinations (argued separately herein), on the grounds that the following phrases or concepts represent new matter:

1. "a disorder associated with damage to, or loss of, brain cells in a mammal" in claims 57, 81, and 85;
2. "wherein said cells are immortal prior to said transplanting and differentiate after said transplanting" in claim 57;
3. "wherein said transplanting improves brain function of said mammal" in claims 57 and 81;
4. "a disorder associated with damage to, or loss of, brain cells in the hippocampus of said mammal" in claim 58;
5. "wherein said transplanting improves cognitive function of said mammal" in claims 57 and 81; and
6. treating a "human", as recited in claims 82 and 86.

Appellants respectfully submit that claims 57, 58, 81, 82, 85, and 86 do not constitute new matter. Support for the phrase "a disorder associated with damage to, or loss of, brain cells

in a mammal", which is recited in claims 57, 81, and 85, can be found throughout the subject application, and particularly at page 1, lines19-25, and page 5, lines 15-22, of the specification as originally filed. The specification states that when transplanted, "pluripotent neuroepithelial cells appear to respond to signals from the damaged or diseased brain by taking up a phenotype that is able to replace or compensate for functional deficits to which the damage or disease otherwise leads" and that "the phenotype of the differentiated cells may be the same as the phenotype of the damaged or lost cells, however, the differentiated cells may be of a different phenotype" and "the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells." At page 2, lines 14-17, the specification states that "the treatment may be carried out on any mammal." Thus, it is clear that the phrase "a disorder associated with damage to, or loss of, brain cells in a mammal", found in claims 57, 81, and 85 is adequately supported.

Support for the phrase "wherein said cells are immortal prior to said transplanting and differentiate after said transplanting", which is recited in claim 57, can be found, for example, at page 5, lines 10-15 and lines 32-36, and page 6, lines 1-10 and 16-25, of the specification as originally filed. At page 5, lines 10-15, the specification states that "when conditionally immortal pluripotent neuroepithelial cells are implanted into a damaged brain the cells differentiate into the correct form of cell required to repair the damage and the differentiated cells are able to form the appropriate connections required to improve function" and that "conditionally immortal cells are cells which are immortal under certain permissive conditions but are not immortal under nonpermissive conditions". Thus, as explained at page 6, lines 6-10, of the specification, "if the conditions under which the cells are maintained are switched to nonpermissive conditions, the development of the cells is allowed to continue. If the correct conditions are provided the cells will continue to develop and will differentiate". As stated at page 6, lines 16-25, of the specification, "conditionally immortal cells have the advantages of immortal cells in that they are "frozen" in the desired stage of development, are easily maintained and multiply well when under permissive conditions but they may be used in transplants as long as the environment into which they are transplanted has nonpermissive conditions." Thus, it is clear that the phrase "wherein said cells are immortal prior to said transplanting and differentiate after said transplanting", found in claim 57, is adequately supported.

Support for the phrase "wherein said transplanting improves brain function of said mammal", which is recited in claims 57 and 81, can be found, for example, at page 8, lines 1-5, which states that the transplanted cells are able to "differentiate in response to the local microenvironment, into the necessary phenotype or phenotypes to improve or restore function." At page 1, lines 18-23, the specification states that when transplanted into a damaged or diseased brain, "pluripotent neuroepithelial cells appear to respond to signals from the damaged or diseased brain by taking up a phenotype that is able to replace or compensate for functional deficits to which the damage or disease otherwise leads". Furthermore, at page 8, lines 21-27, the specification states that, "preferably, the treatment will substantially correct a behavioral and/or psychological deficit ... [H]owever, treatment according to the present invention ... may lead to improvement in function without complete correction." Page 10, lines 34-36, and page 11, lines 1-7, state

> Thus it appears that the cell lines are capable of responding to damage-associated signals so as to differentiate into cells, of one or more types, that are able re-establish the necessary connections and restore the functions(s) discharged by the damaged tissue. It is this capacity that provides both a strategy and a material basis for transplant therapies with which to target a wide range of behavioral and psychological deficits consequent upon an equally wide range of forms of damage to the human brain....

Thus, it is clear that the phrase "wherein said transplanting improves brain function of said mammal", found in claims 57 and 81, is adequately supported.

Support for the phrase "a disorder associated with damage to, or loss of, brain cells in the hippocampus of said mammal", which is recited in claim 58, can be found, for example, at page 5, lines 15-22, page 13, lines 2-4, and Examples 5-9 at pages 22-29, of the specification as originally filed. At page 5, lines 15-22, the specification indicates that the implanted cells take up a phenotype that is capable of functionally integrating and compensating for damaged or lost cells. As described in Example 5 at page 22 of the specification, ischemic lesions were created in the CA1 area of the hippocampus of rats and restoration of spatial learning and memory was evaluated using the Morris water maze test. In Example 9, at pages 27-29, the specification describes assessment of post-mortem ischaemic brain damage, and indicates ischemia was present in the hippocampus of the animal model (see, for example, page 28, lines 1-2). As

indicated at page 9, lines 29-35, and page 10, lines 1-9, the lesion-and-behavior model used in Examples 5-9 uses a technique of four-vessel occlusion (4 VO), "causing relatively circumscribed and specific damage to the CA1 pyramidal cells of the dorsal hippocampus, along with a cognitive deficit...". The Examiner also acknowledged that the '274 application teaches treatment of damage in the hippocampus. The Office Action dated May 25, 2004 states "the specification is limited to treating damage to hippocampal cells using hippocampal, pluripotent, nestin-positive, neuroepithelial cells" (page 14, lines 18-19; emphasis added); and "therefore, the claims should be limited to treating damage to hippocampal brain cells using hippocampal, pluripotent, nestin-positive, neuroepithelial cells" (page 15, lines 2-3; emphasis added). Thus, it is clear that the phrase "a disorder associated with damage to, or loss of, brain cells in the hippocampus of said mammal", found in claim 58, is adequately supported.

The Advisory Action dated December 21, 2004 states that the phrase "wherein said transplanting improves cognitive function of said mammal", as recited in claims 57 and 81, is new matter. Appellants submit that this aspect of the rejection appears inconsistent with the basis of the rejection offered at page 4 of the Advisory Action, which states "the specification does not support improving any 'brain function' as newly amended by adding neuroepithelial cells because the specification only taught using a model of cognitive function" (emphasis added). The Examiner also acknowledged that evaluation and/or improvement in cognitive function is taught in the specification elsewhere during prosecution; see, for example, page 7, lines 12-13, of the Office Action dated August 20, 2003; and page 6, line 15, page 12, lines 17-18, and page 15, lines 20-21, of the Office Action dated May 25, 2004. Page 15, lines 220-21 states "the specification taught using mouse, pluripotent, nestin-positive, hippocampal neuroepithelial cells to restore cognitive function in rats" (emphasis added). Thus, it is clear that the phrase "wherein said transplanting improves cognitive function of said mammal", found in claims 57 and 81, is adequately supported.

Support for the phrase "wherein said transplanting improves cognitive function of said mammal", recited in claims 57 and 81, can be found, for example, at page 8, lines 15-27, of the specification as originally filed, which states:

> After treatment the progress of the patient may be monitored using behavioral and/or psychological tests and/or, if desired, tests which monitor brain activity in selected areas of the brain. For example, tests for cognitive function may be performed before and after transplantation.

> Preferably, treatment will substantially correct a behavioral and/or psychological deficit. However, that may not always be possible. Treatment according to the present invention and with the cells, medicaments and pharmaceutical preparations of the invention, may lead to improvement in function without complete correction. Such improvement will be worthwhile and of value. (emphasis added)

Furthermore, at page 9, lines 29-35, and page 10, lines 1-9, the '274 application teaches that the lesion-and-behavior model used in Examples 5-9 of the application causes a cognitive deficit due to loss of blood supply to the brain. The Morris water maze test was used to evaluate improvement in cognitive function. Thus, it is clear that the phrase "wherein said transplanting improves cognitive function of said mammal", found in claims 57 and 81, is adequately supported.

Support for the treatment of humans, as recited in claims 82 and 86, can be found throughout the specification, where it is clear that treatment of humans was contemplated. For example, at page 2, lines 14-17, the specification as originally filed indicates that "treatment may be carried out on any mammal but the present invention is especially concerned with the treatment of humans, especially treatment with human cells, and with human cells and cell lines" (emphasis added). At page 4, lines 1-3, the specification as originally filed indicates "a further aspect of the invention provides for conditionally immortal, pluripotent, neuroepithelial cells for therapeutic use, especially in humans" (emphasis added). At page 7, lines 8-10, the specification indicates "the cells used in the treatment of humans should preferably be derived from human cells to reduce problems with immune rejection" (emphasis added). Thus, it is clear that treatment of humans, recited in claims 57 and 81, is adequately supported.

Contrary to the statements at page 4 of the Advisory Action, Appellants respectfully submit that the specification as a whole does support using neuroepithelial cells other than hippocampal neuroepithelial cells. At page 13, lines 5-7, the specification teaches that "the part of the fetal brain from which the neuroepithelial cells are taken and the precise time (stage and development) may vary". Furthermore, as indicated at page 12, lines 33-36, and page 13, lines 1-4, uses of cells according to the invention are not limited to repair of the particular type of damage modeled in Examples 6, 7, and 8; rather, "transplantation into any area of the brain is envisaged with consequent improvement in function". Examples of diseases or conditions that

result in behavioral and/or psychological deficits that may be treated in accordance with the present invention are set forth at page 3, lines 1-14, of the specification as originally filed.

The subject matter of a claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement. "It is not necessary that the application describe the claim limitations exactly,...but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations". *In re Wertheim*, 541 F.2d 257, 262; 191 USPQ 90, 96 (C.C.P.A. 1976). "*Ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." *Fujikawa v. Wattanasin*, 93 F.3d 1559; 39 USPQ2d 1895, 1904 (Fed. Cir. 1996), quoting from *In re Edwards*, 568 F.2d 1349, 1351-52; 196 USPQ 465, 467 (CCPA 1978). Appellants respectfully submit that the specification provides adequate support for the claimed subject matter, describing the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed subject matter, which is all that is required to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. The claimed subject matter does not represent new matter. Accordingly, Appellants request that this rejection of the claims under 35 U.S.C. §112, first paragraph, be reversed.

C. The specification enables a method for treating a disorder associated with damage to, or loss of, brain cells in a mammal by intracerebrally transplanting pluripotent, nestin-positive, neuroepithelial cells into the brain of the mammal, wherein the cells have been genetically modified to be conditionally immortal, wherein the cells are immortal prior to transplantation and differentiate after transplantation, and wherein transplantation improves brain function of the mammal, as recited in claims 57, 58, 60-62, and 76-86.

1. Appellants' specification, which broadly teaches that pluripotent, nestin-positive neuroepithelial cells may be obtained from various areas of the brain and intracerebrally transplanted to treat a disorder associated with damage to, or loss of, brain cells, and exemplifies using mouse hippocampal

pluripotent, nestin-positive neuroepithelial cells to treat a cognitive deficit associated with damage to, or loss of brain cells in the hippocampus, enables claims that are not limited to transplantation of mouse hippocampal cells to treat a cognitive deficit associated with damage to, or loss of hippocampal cells.

Appellants submit that, given the benefit of the specification's disclosure, a person of ordinary skill in the art could readily identify and use nestin-positive, pluripotent neuroepithelial cells as recited in the claims. Evidence of the ability to use a variety of pluripotent, nestin-positive neuroepithelial cells to treat various intracerebral tissues is provided within Exhibit D, which accompanied the Sinden Declaration, described above. Exhibit D describes an experiment carried out using human nestin-positive pluripotent neuroepithelial cells derived from the human fetal cortex, to treat damage associated with the basal forebrain. These cells were genetically modified to be conditionally immortal, in accordance with Appellants' teachings, and as recited in the currently pending claims. As indicated above, Appellants respectfully submit that the teachings of the specification and Exhibit D are consistent, and the human nestin-positive neuroepithelial cells described in Exhibit D correlate with the teachings of the subject specification as originally filed. As indicated at page 13, lines 5-7 of the '274 application, the region of the brain from which neuroepithelial cells are obtained and the precise time (stage and development) they are obtained may vary.

The Sinden *et al.* publication (*Neuroscience*, 81:599-608, 1997) was cited in the Office Action dated May 25, 2004 and previous Actions as suggesting that CA1 cells derived from the hippocampus must be used to repair damaged CA1 hippocampal tissue. However, the cited portion of the Sinden *et al.* (1997) reference is merely characterizing the prior art. As indicated in the Sinden Declaration, "the statement referred to by the Reviewer within the Sinden *et al.* publication (of which I am the first author), is made with respect to a previous study that used primary cells that were mature, differentiated or committed CA1 cells, and not the conditionally immortal, pluripotent, nestin-positive, neuroepithelial cells that are used in the method of our invention" (emphasis added).

As indicated in the Sinden Declaration, "provided the neuroepithelial cells are nestin-positive and retain the ability to differentiate into the specified phenotypes in response to

environmental signals, they are appropriate for use in the present invention." The Scheffler *et al.* publication does not provide any reason to doubt that one of ordinary skill in the art, having the benefit of the specification's disclosure, can determine what is, and what is not, an appropriate pluripotent neuroepithelial cell for use in the subject invention.

While Appellants acknowledge that some experimentation and screening may be required to isolate human, pluripotent, nestin-positive neuroepithelial cells, the court in *In re Wands* has stated

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'.
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731; 8 USPQ2d 1400 (Fed. Cir. 1988).

The cells recited in the claimed methods are positive for the progenitor cell marker, nestin. As indicated in the Sinden Declaration, "nestin-positive cells can be readily identified using immunocytochemistry," as described at pages 20 and 21 of the subject patent application, or by other techniques known to those of ordinary skill in the art. Furthermore, Example 4 of the '274 application describes an *in vitro* screening method for determining the pluripotency of the cells *in vivo* (see page 13, lines 23-26). The experimentation and screening required to obtain the necessary pluripotent, nestin-positive neuroepithelial cells are standard and routine in the art. Thus, Appellants respectfully submit that the '274 application provides adequate guidance for the skilled person to identify and use appropriate cells, without resort to undue experimentation.

2. Appellants' specification, which broadly teaches that conditionally immortal pluripotent, nestin-positive neuroepithelial cells may be transplanted to any portion of the brain, and exemplifies transplanting conditionally immortal pluripotent, nestin-positive neuroepithlial cells to the

hippocampus, enables claims that are not limited to transplantation to the hippocampus.

The Scheffler *et al.* publication (*Trends in Neurosci.*, Vol. 22, pg. 348-357, 1999) has been cited in the Office Action dated May 25, 2004 (page 17) and earlier Actions as showing that it was "unpredictable" how to target particular areas of the brain when transplanting neural cells. However, the relevant passage in the Scheffler *et al.* publication refers to a study that used transplanted post-natal and adult neurons (therefore, differentiated neurons), and did not relate to the transplantation of conditionally immortal pluripotent neuroepithelial cells. As indicated in the Sinden Declaration, "one of the great advantages of the present invention is that it is not necessary to target particular areas of the brain to correct cell damage." This is emphasized at various points throughout the '274 application, as well (see, for example, page 5, lines 10-31). As Dr. Sinden explains in his Declaration,

> previously, it was thought that to treat damage in a developed postnatal or adult brain, it was necessary to use tissue/cells derived from the same area as that damaged. Importantly, prior to our invention, even if the cells to be transplanted were taken from a fetus, ... the cells would typically be committed to a particular phenotype. Moreover, prior to our work, there was no selection of nestin-positive, pluripotent cells, or genetic modification of the cells to confer conditional immortality such that the cells would be immortal prior to transplantation but differentiate subsequent to transplantation (page 2 of the Sinden Declaration).

The inventors realized that, "surprisingly, transplanting cells that were selected to retain a nestin-positive, pluripotent, conditionally immortal phenotype resulted in the repair of damage, and this was independent of the site of damage", as indicated in Dr. Sinden's Declaration. Accordingly, using the cells of the claimed invention permits treatment at different sites of damage with a single cell line, which is selected on the basis of its nestin-positive, pluripotent characteristics, and is genetically modified to be conditionally immortal.

In contrast to the observations made in the Scheffler *et al.* publication, which involved the use of differentiated post-natal and adult neurons, as stated above, Appellants have shown that the targeting of cells is not necessary using the pluripotent cells of the subject invention. The subject specification teaches that the pluripotent cells migrate to areas of damage after transplantation, and become integrated in the damaged areas, effecting repair. The transplanted

cells migrate as necessary, populating the damaged areas of the brain, which overcomes the difficulties highlighted by the Scheffler *et al.* publication relating to the use of differentiated neurons in transplantation. As explained by Dr. Sinden in his Declaration, "this ability of the cells to migrate (which we were the first to observe) is an inherent feature of the cells; therefore, the difficulties identified in the Scheffler *et al.* publication will not be experienced when using nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal" (page 2 of the Sinden Declaration).

It is well settled patent law that an applicant's statements must be accepted as true unless the Patent Office can provide evidence to doubt the truth of those statements. *In re Marzocchi*, 439 F.2d 220; 169 USPQ 367 (CCPA 1971). The Examiner has not provided acceptable reasoning for doubting the statements within the specification or the Declaration by Dr. Sinden. The record is replete with evidence supporting the truth of the '274 application's teachings that the cells of the invention migrate to areas of damage after transplantation, become integrated within the damaged brain, and achieve repair.

At page 17 of the Office Action dated May 25, 2004, the Examiner states "a mere statement that the cells do not require targeting particular areas of the brain without evidence or scientific reasoning is inadequate to overcome the rejection". Appellants assert that more than "a mere statement" has been made of record in support of the ability of the recited cells to migrate to different areas of the brain, integrate, and effect repair. Submitted with the Sinden Declaration as Exhibit B was a copy of U.S. Patent Application Publication No. 2002/0037277 (now U.S. Patent No. 6,569,421; referred to herein as the '277 publication). The example at pages 2-5 of the published application clearly demonstrates migration of the cells, and also shows that cells from one region of the brain (hippocampal region) can repair damage to a different area of the brain, such as cortex and basal ganglia, thus proving the truth of the subject '274 application's teachings.

The cells utilized in the example of the '277 publication were nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims. The Office Action dated May 25, 2004 indicates that "no evidence can be found that the cells in Exhibit B were prepared the same as those described in the specification" (page 18 of the Office Action). Appellants point to paragraph 0030 at column 2 of the '277 publication, which states "conditionally immortal pluripotent neuroepithelial cells

from the MHP36 clonal cell line were prepared as disclosed in WO-A-97/10329" (emphasis added), which is the published PCT application (PCT/GB96/02251) to which the subject '274 application claims priority. The MHP36 clonal cell line is used in the Examples in the '274 application (see, for example, page 8, lines 35-36; page 9, lines 1-29; page 10, lines 23-36; page 11, lines 1-9; pages 15-16; and pages 19-29 of the '274 application).

As indicated in the Sinden Declaration, regarding the '277 publication, "compelling evidence of extensive migration is presented at page 4, paragraph 0047, which indicates that contralaterally grafted cells 'migrated across the midline to the opposite side of the brain (emphasis added)'." The Office Action dated May 25, 2004 indicates that page 4, paragraph 0047, of the '277 publication "merely discusses migration and does not state adequate numbers of cells migrated to the site of tissue damage such that the cognitive deficit was treated" (page 18 of the Office Action). The '277 publication indicates that migration of implanted cells was extensive (see paragraphs 0047 – 0049). The issue of the number of migrating cells in the experiment is of limited relevance, since functional recovery was confirmed. Appellants point to pages 4 and 5, paragraphs 0050 – 0053, of the '277 publication. The stated purpose of the experiments was to determine whether grafts of MHP36 cells, from a conditionally immortalized clonal line, would promote functional recovery from stroke damage when placed in the intact hemisphere contra-lateral to the infarct cavity (see paragraph 0050 at page 4 of the '277 publication). As indicated in paragraphs 0050 and 0051 of the '277 publication, "the findings indicate that both sensorimotor and motor asymmetries were normalized in rats with grafts initially sited in the intact hemisphere...The evidence for recovery of sensorimotor and motor functions is robust, because improvements were seen over an extended time period."

Appellants note that the currently pending claims recite that transplanting the cells improves brain function (*e.g.*, cognitive function) in the mammal. Thus, it would be understood by those skilled in the art that the number of cells transplanted would be an amount effective to achieve the recited improvement in function. Guidance regarding the number of cells to be transplanted is provided page 8, lines 28-34, of the '274 application as originally filed.

The Snyder *et al.* patent (U.S. Patent No. 6,528,306), of record, describes the migratory properties of neural stem cells and demonstrates that the cells can be maintained in culture in an undifferentiated state, with differentiation occurring upon transplantation. The Snyder *et al.* patent was not publicly available at the priority date of the subject application; however, the

patent demonstrates that the '274 application contained all the information necessary for the skilled person to carry out the invention. The background section of the Snyder *et al.* patent cites several early scientific papers reporting the behavior exhibited by neural stem cells upon transplantation. For example, at column 1, lines 44-56, the Snyder *et al.* patent indicates that neural stem cells are extremely plastic and can migrate and differentiate "in a temporally and regionally appropriate manner ..., responding similarly to local microenvironmental cues for their phenotypic determination and appropriately differentiating into diverse neuronal and glial cell types." Furthermore, at column 1, lines 40-43, the Synder *et al.* patent cites several early publications as demonstrating the behavior of pluripotent neural stem cells following transplantation, including their ability to interact with host cells and differentiate appropriately.

Accordingly, Appellants respectfully submit that the scope of enablement provided by the subject '274 application bears a reasonable correlation to the scope of the claims; the '274 application enables claims that are not limited to transplantation to the hippocampus.

3. Appellants' specification, which broadly teaches that conditionally immortal pluripotent, nestin-positive neuroepithelial cells may be intracerebrally transplanted into a mammal, such as a human, to treat a disorder associated with damage to, or loss of, brain cells, and exemplifies transplanting conditionally immortal pluripotent, nestin-positive neuroepithlial cells to a rat model, enables claims that are not limited to transplantation to a rat.

Claims 57, 58, 60-62, and 76-84 recite a method for treating a disorder associated with damage to, or loss of, brain cells in a mammal. Claim 85 recites a method for treating a cognitive deficit caused by damage to the hippocampus of a mammal. Claims 64, 82, and 86 specify that the mammal is human.

In the Office Action dated May 25, 2004, the Examiner states "any new enablement rejections below have been made because of the increased breadth of the claim 57 and the breadth of new claims 81 and 85 ... Applicants claim a method of treating a human using neural stem cells expressing nestin and capable of self-renewal, but have not linked cells having such a

phenotype to the ability to treat cognitive deficits in humans" (page 12, lines 9-13, of the Office Action).

Appellants are again perplexed by the apparent inconsistency in the Examiner's maintenance of this aspect of the rejection. In the Office Action dated December 23, 2002, claims 57-67 were rejected under 35 U.S.C. §112, first paragraph, as non-enabled. Claim 57 recited "a method of treating a cognitive deficit in a mammal, said method comprising intracerebrally transplanting pluripotent, nestin-positive, neuroepithelial cells into said mammal, wherein said cells have been genetically modified to be conditionally immortal, wherein said cells are immortal prior to said transplantation but differentiate after said transplantation, and wherein said transplantation improves cognitive function in said mammal." At page 7 of the Office Action dated December 23, 2002, the Examiner states "the rejection regarding the breadth of 'animal' has been withdrawn because the claims have been amended to 'mammal' and because the rats having a lesion in the hippocampus used throughout the specification were treated with mouse cells."

Appellants respectfully assert that the animal model exemplified in Examples 5-9 of the '274 application is predictive of the applicability of the claimed invention to other mammals, including humans. Furthermore, experimental data has been made of record in the '274 application that confirms the efficacy of the conditionally immortal nestin-positive neuroepithelial cells in treating primates, including marmosets and humans. In experiments described by Virley *et al.* (*Brain*, 1999, 122:101-115), which accompanied the Sinden Declaration as Exhibit C, pluripotent MHP36 cells (mouse cells exemplified in the '274 application) were transplanted to the brains of marmosets (a primate). As indicated at pages 3-4 of Dr. Sinden's Declaration, "these cells performed as well within the marmoset brain as the marmoset fetal allografts, which suggests a low immune response provocation and confirms the applicability of our invention to treat primates, including humans, with a reasonable expectation of success" (see paragraph bridging pages 111-112 of the Virley *et al.* publication).

Experimental data demonstrating transplantation of human cells in a rat model of brain damage has also been made of record. The human cells used in the experiment described in Exhibit D express both nestin (intermediate filament marker) and musashi 1. As indicated in Exhibit D, nestin and musashi 1 are both phenotypic markers for neuroepithelial stem cells. The musashi 1 marker was more recently identified than nestin and, hence, merely confirms the neural

epithelial status of the cells, as also determined by nestin expression. As indicated above with regard to the rejection for lack of written description, the Kawaguchi *et al.* and Sakakibara *et al.* publications are of record. The Sakakibara *et al.* publication indicates that musashi is a binding protein that is expressed in neural precursor cells, which can be used to identify precursor cells. As indicated in the abstract of the Sakakibara *et al.* publication, the musashi family of proteins are evolutionarily conserved across species. In mammals, musashi 1 and musashi 2 are strongly co-expressed in neural precursor cells, including CNS stem cells. Likewise, the Kawaguchi *et al.* publication demonstrates that nestin is expressed in neural precursor cells. Use of musashi 1 is equivalent to use of nestin for identifying neural precursor cells. Thus, detection of musashi 1 expression, in addition to detection of nestin expression, is not "essential" or "required". One of ordinary skill in the art would appreciate that musashi 1 expression does not represent a characterizing feature of the cells that had to be discovered before the invention could be carried out; demonstrating the expression of nestin by the cells, as taught in the specification, is sufficient. The mere fact that the human cells were further characterized and it was determined that the cells expressed musashi 1, in addition to nestin, should not disqualify the experimental results and accompanying Declaration by Dr. Sinden as probative evidence in the determination of enablement under 35 U.S.C. 112, first paragraph.

Thus, the subject '274 application describes a working example involving the transplantation of mouse cells in a rat model of brain damage characterized by damage to, or loss of, brain cells (Examples 5-9). Appellants have also submitted experimental data describing: (i) transplantation of mouse cells in a primate (marmoset) model of brain damage characterized by damage to, or loss of, brain cells (the Virley *et al.* publication; Exhibit C); and (ii) transplantation of human cells in a rat model of brain damage characterized by damage to, or loss of, brain cells (Exhibit D). The record is replete with evidence of the versatility of the claimed methods to treat the recited genus of mammals, including humans. Accordingly, Appellants respectfully submit that the scope of enablement provided by the subject '274 application bears a reasonable correlation to the scope of the claims.

4. Appellants' specification, which broadly teaches that pluripotent, nestin-positive neuroepithelial cells may be genetically modified to be conditionally immortal, such that the cells are immortal prior to

transplantation and differentiate after transplantation, and exemplifies transduction with a temperature-sensitive simian virus 40 large T antigen under the control of an interferon-inducible H-2K^b promoter, enables claims that are not limited to the temperature-sensitive simian virus 40 large T antigen under the control of the interferon-inducible H-2K^b promoter.

The Office Action dated May 25, 2004 indicates that the '274 application does not provide sufficient guidance for conferring conditional immortality to cells (for example, via the temperature sensitive oncogene (tsA58)). As taught in the '274 application, such conditionally immortal cells can be readily prepared by transduction of an oncogene into a cell (see, for example, page 6 of the specification). As taught at page 7, lines 1-7, of the '274 application, the use of non-human transgenic animals is but one method for obtaining conditionally immortalized cells. Conditional immortality is described on page 5, last paragraph, and pages 6 and 7 of the '274 application, and it is clear that the cells remain immortal (undifferentiated and continuously dividing) under one set of conditions, but can be induced to mature and differentiate (losing immortality) by a change in conditions. Page 12, lines 23-31, of the '274 application states:

> It should be understood that although the experiments described in the Examples below have been carried out using the ts SV40 large T antgen gene to confer conditional immortality on the cells, any other gene which is capable of causing conditional immortality may be used. Such genes may be constructed from known oncogenes. For example, a conditionally immortal gene has been constructed from the c-myc oncogene and is described by Hoshimaiuaru et al, 1996.

The Frederiksen *et al.* publication (*Neuron*, 1998, Vol. 1, 439-448) and Jat *et al.* publication (*Proc. Natl. Acad. Sci. USA*, 1991, 88:5096-5100), of record, which accompanied the Amendments submitted on September 30, 2002 and March 20, 2003, respectively, show that methods for achieving conditional immortality using, for example, the temperature-sensitive SV40 oncogene, were known in the art even in 1988. The background section of the Snyder *et al.* patent also highlights methods (both epigenetic and genetic) for immortalizing cells that are not dependent on the large T antigen temperature-sensitive oncogene (see column 1, lines 31-43 of the Snyder *et al.* patent). Therefore, Appellants respectfully assert that the specification fully enables the use of pluripotent, nestin-positive neuroepithelial cells, including human cells, which have been genetically modified to be conditionally immortal, as recited in the claims.

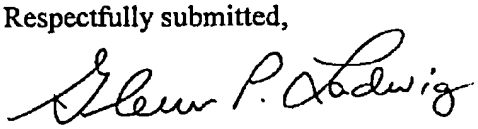
To exemplify their invention, Appellants used a widely applicable conditional immortalization method known to those skilled in the art as of the filing date. Although the temperature-sensitive simian virus 40 large T antigen under the control of an interferon-inducible H-2K^b promoter was the genetic construct used by Appellants in demonstrating the truth of their teachings that nestin-positive, pluripotent neuroepithelial cells genetically modified to be conditionally immortal could be intracerebrally transplanted to treat a disorder associated with damage to, or loss of, brain cells, they clearly and unambiguously taught that additional methods of conditional immortalization could be used. They clearly indicated that the method of conditional immortalization is not essential to the invention. Rather, any gene known to effectively cause conditional immortality can be used in accord with Appellants' teachings. It is inequitable that Appellants' claims should be so limited that as newer immortalization technology becomes available, it provides a way around the claimed invention, which is not restricted to one type of conditional immortalization protocol over another.

Appellants respectfully submit that a person skilled in the art, having the benefit of the specification's disclosure, could readily make and use the claimed invention without resort to undue experimentation. Accordingly, Appellants request that this rejection of the claims under 35 U.S.C. §112, first paragraph, be reversed.

CONCLUSION

In view of the foregoing, Appellants urge that the Board overrule the outstanding rejections under 35 U.S.C. §112, first paragraph, and that this application be passed to issuance.

Respectfully submitted,



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Attachments: Appendix A: Claims Appendix
Appendix B: Evidence Appendix

APPENDIX A

Currently Pending Claims

(Claims 1-48, 59, and 68-75 cancelled in Amendment dated February 20, 2004)
(Claims 49-56 cancelled in Amendment dated September 30, 2002)
(Claims 63 and 65-67 cancelled in Amendment dated March 20, 2003)

Claim 57. A method for treating a disorder associated with damage to, or loss of, brain cells in a mammal, said method comprising intracerebrally transplanting pluripotent, nestin-positive, neuroepithelial cells into the brain of said mammal, wherein said cells have been genetically modified to be conditionally immortal, wherein said cells are immortal prior to said transplanting and differentiate after said transplanting, and wherein said transplanting improves brain function of said mammal.

Claim 58. The method of claim 57, wherein the disorder is associated with damage to, or loss of, brain cells in the hippocampus of said mammal.

Claim 60. The method of claim 57, wherein said pluripotent, nestin-positive, neuroepithelial cells are cells of a clonal cell line.

Claim 61. The method of claim 57, wherein said method further comprises culturing said pluripotent, nestin-positive, neuroepithelial cells in serum-free medium prior to said transplanting.

Claim 62. The method of claim 57, wherein the disorder is the result of hypoxia.

Claim 64. The method of claim 57, wherein said mammal is a human.

Claim 76. The method of claim 57, wherein the disorder comprises a cognitive deficit, and wherein the brain function comprises cognitive function.

Claim 77. The method of claim 57, wherein the genetic modification comprises transduction with a temperature-sensitive oncogene.

Claim 78. The method of claim 57, wherein the genetic modification comprises transduction with a temperature-sensitive simian virus 40 large T antigen gene.

Claim 79. The method of claim 57, wherein the genetic modification comprises transduction with a temperature-sensitive simian virus 40 large T antigen gene under the control of an interferon-inducible H-2K^b promoter.

Claim 80. The method of claim 57, wherein said cells are immortal at 33° C and differentiate at 39° C.

Claim 81. A method for treating a disorder associated with damage to, or loss of, brain cells in a mammal, said method comprising intracerebrally transplanting human pluripotent, nestin-positive neuroepithelial cells into the brain of said mammal, wherein said human pluripotent, nestin-positive neuroepithelial cells comprise a temperature-sensitive simian virus 40 large T antigen gene, and wherein said transplanting improves brain function of said mammal.

Claim 82. The method of claim 81, wherein said mammal is human.

Claim 83. The method of claim 81, wherein said cells are immortal at 33° C and differentiate at 39° C.

Claim 84. The method of claim 81, wherein said temperature-sensitive simian virus 40 large T antigen gene is under the control of an interferon-inducible H-2K^b promoter.

Claim 85. A method for treating a cognitive deficit caused by damage to the hippocampus of a mammal, said method comprising intracerebrally transplanting human pluripotent, nestin-positive, hippocampal neuroepithelial cells into said hippocampus of said

mammal, wherein said human pluripotent, nestin-positive, hippocampal neuroepithelial cells comprise a temperature-sensitive simian virus 40 large T antigen gene under the control of an interferon-inducible H-2K^b promoter, and wherein said transplanting improves cognitive function in said mammal.

Claim 86. The method of claim 85, wherein said mammal is human.

Appendix B

1. Declaration of Dr. John Sinden under 37 C.F.R. §1.132, including Exhibits A-D, of record, which accompanied the Amendment submitted on September 30, 2002, and which were entered into the record in the Office Action dated December 23, 2003.

2. Copy of published article by Kawaguchi *et al.* (*Molecular and Cellular Neuroscience*, 2001, 17:259-273), which accompanied the Response submitted on October 21, 2004, and was entered into the record in the Advisory Action dated December 21, 2004.

3. Copy of published article by Sakakibara *et al.* (*PNAS*, 2002, 99(23):15194-15199), which accompanied the Response submitted on October 21, 2004, and was entered into the record in the Advisory Action dated December 21, 2004.

4. Copy of U.S. Patent No. 6,528,306 (Snyder *et al.*), which accompanied the Response submitted on February 20, 2004, and was entered into the record in the Office Action dated May 25, 2004.

5. Copy of published article by Jat *et al.* (*Proc. Natl. Acad. Sci. USA*, 1991, 88:5096-5100), which accompanied the Response submitted on March 20, 2003, and was entered into the record in the Office Action dated May 25, 2004.

6. Copy of published article by Frederiksen *et al.* (*Neuron.*, 1988, 1:439-448), which accompanied the Response submitted on September 30, 2002, and was entered into the record in the Office Action dated May 25, 2004.